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CAVUM SEPTI PELLUCIDI IN TOURETTE SYNDROME

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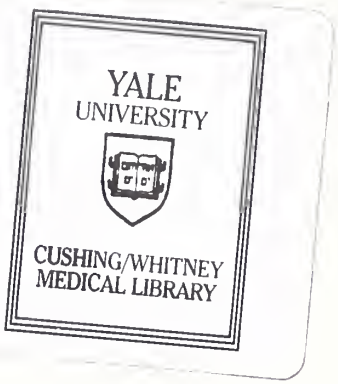
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Cavum Septi Pellucidi in Tourette Syndrome

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Karen J. Kim
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CAVUM SEPTI PELLUCIDI IN TOURETTE SYNDROME.

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An enlarged cavum septi pellucidi (CSP) has been associated with a variety of neuropsychiatric disorders and is a putative marker of disturbed brain development. The goal of this study was to characterize systematically the CSP and the related cavum vergae in individuals with Tourette Syndrome (TS). The overall size and anteroposterior length of the CSP in 161 children (97 with TS and 64 normal pediatric controls) and 107 adults (43 with TS and 64 normal adult controls) were rated on high-resolution magnetic resonance images in the coronal view. The associations of CSP size with diagnosis and symptom severity scores were assessed using ordinal logistic regression analysis.

CSP size in TS children was significantly smaller than in normal control subjects and was inversely associated with ADHD symptom severity in the TS subjects. CSP size was not significantly associated with the comorbid diagnoses of OCD or ADHD. These results were replicated in an independent sample of TS and normal control adults. The presence of a cavum vergae was not significantly associated with a diagnosis of TS. These findings suggest that the pathophysiology of TS may involve abnormalities in the early development of the CSP or in the neighboring corpus callosum, septal nuclei, or related portions of the limbic system.

Acknowledgements

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INTRODUCTION

The cavum septi pellucidi (CSP) is a potential midline space bounded by the two leaves of the septum pellucidum. The CSP or related cavum vergae (CV) that persist postnatally are putative markers of disturbances in early brain development (1-3). An increased size or prevalence of the CSP has been reported in a wide variety of clinical populations, including children with mental retardation (4) or fetal alcohol syndrome (5), in individuals with affective disorders (6), and most commonly in patients with schizophrenia (7, 8).

Tourette Syndrome (TS) is characterized by motor and vocal tics that begin in childhood and that fluctuate over time. It is frequently associated with other social and behavioral disturbances (9, 10). In both clinical and epidemiological samples, TS co-occurs with Obsessive-Compulsive Disorder (OCD) or Attention-Deficit/Hyperactivity Disorder (ADHD) (9, 11-14). The co-occurrence of these disorders is thought to be a consequence of shared genetic and environmental risk factors that produce anatomical and functional disturbances in cortical-subcortical circuitry (15, 16). Pre- and perinatal risk factors such as maternal stress, low birth weight, and obstetric complications associated with CNS hypoxia or ischemia have been hypothesized in TS to play a role in modulating both symptom severity and the likelihood of having comorbid OCD or ADHD (17-20). The anatomical connectivity of the septal region that surrounds the CSP is intimately related to this cortical-subcortical circuitry. Characterizing the septal region may therefore provide important information in these patient populations concerning disturbances in the anatomical and functional development of these circuits. Isolated case reports have suggested that the CSP may be enlarged in tic disorders (21-23).

STATEMENT OF PURPOSE

The main objective of our study was to characterize the occurrence and size of CSP in individuals with TS. We hypothesized that the CSP differs significantly in size in subjects with TS compared to normal controls. The presence of CSP and CV was evaluated in MRI scans from 140 individuals with TS and 128 normal control subjects. In addition, correlations of CSP size with the severity of tic, OCD, and ADHD symptoms were examined in the patient group.

METHODS

Subject Recruitment and Characterization

Subjects with TS (97 children and 43 adults) were recruited from the Tic and Obsessive-Compulsive Disorders Specialty Clinic at the Yale Child Study Center. Normal controls (64 children and 64 adults) were recruited from a list of families in the local community purchased from a telemarketing company. These individuals were identified as being within a specified age range and as living in the same neighborhoods (based on zip code) as the TS subjects. Individuals from the list were randomly selected for contact. Introductory letters were sent and followed by screening phone calls. Of the eligible control subjects contacted, approximately 10% participated. After complete description of the study to the subjects, written informed consent was obtained. Each child subject's assent was also obtained.

Subjects were aged 5 to 63 years, and they were predominantly right-handed (24). Subjects included individuals with a primary diagnosis of TS with or without comorbid OCD or ADHD, and normal controls. A DSM-IV diagnosis of TS was based on an extensive clinical examination (B. Peterson and L. Scahill). Comorbid neuropsychiatric diagnoses were established through administration of the Schedule for Tourette Syndrome and Other Behavioral Disorders (STOBS) (25), a structured interview which includes the Kiddie-Schedule for Affective Disorders and Schizophrenia Epidemiologic Version, the adult Schedule for Affective Disorders and Schizophrenia (26, 27), and more detailed sections on TS and OCD for both children and adults (28). Exclusionary criteria for TS subjects included another movement disorder or a major psychiatric disorder other than OCD or ADHD that antedated the onset of tics. For all control subjects,

exclusionary criteria included any history of tic disorder, OCD, ADHD, or current Axis I disorder. Additional exclusionary criteria for both groups included a history of seizure or head trauma with loss of consciousness, ongoing substance abuse or previous substance dependence, or IQ below 80.

At the time of the study, 59 child TS subjects (61%) were taking psychotropic medication that included typical neuroleptics (n=15), atypical neuroleptics (n=3), stimulants (n=4), alpha-agonists (n=21), serotonin-specific reuptake inhibitors (n=8), or tricyclic antidepressants (n=7). Of the adult TS subjects, 27 (63%) were taking medication, which included typical neuroleptics (n=3), atypical neuroleptics (n=1), alpha-agonists (n=4), serotonin-specific reuptake inhibitors (n=9), or tricyclic antidepressants (n=1).

Ratings of current (at the time of scan) and worst-ever severity of tic and OCD symptoms were obtained using the Yale Global Tic Severity Scale (29) and either the adult or child version of the Yale-Brown Obsessive Compulsive Scale (30, 31). The Child Behavior Checklist (CBCL) (32) and the Conners Parent and Teacher Rating Scales (33) scores were obtained for subjects under 18 years of age. Ratings of ADHD symptom severity both at the time of scanning and prior to initiating medication were obtained using the ADHD rating scale (34). Socioeconomic status at birth was estimated using the Hollingshead Four-Factor Index of Social Status (35).

MRI Scanning

Magnetic resonance images (MRI's) of the brain were obtained using a single GE Signa 1.5-Tesla scanner (General Electric, Milwaukee, WI). Head position was

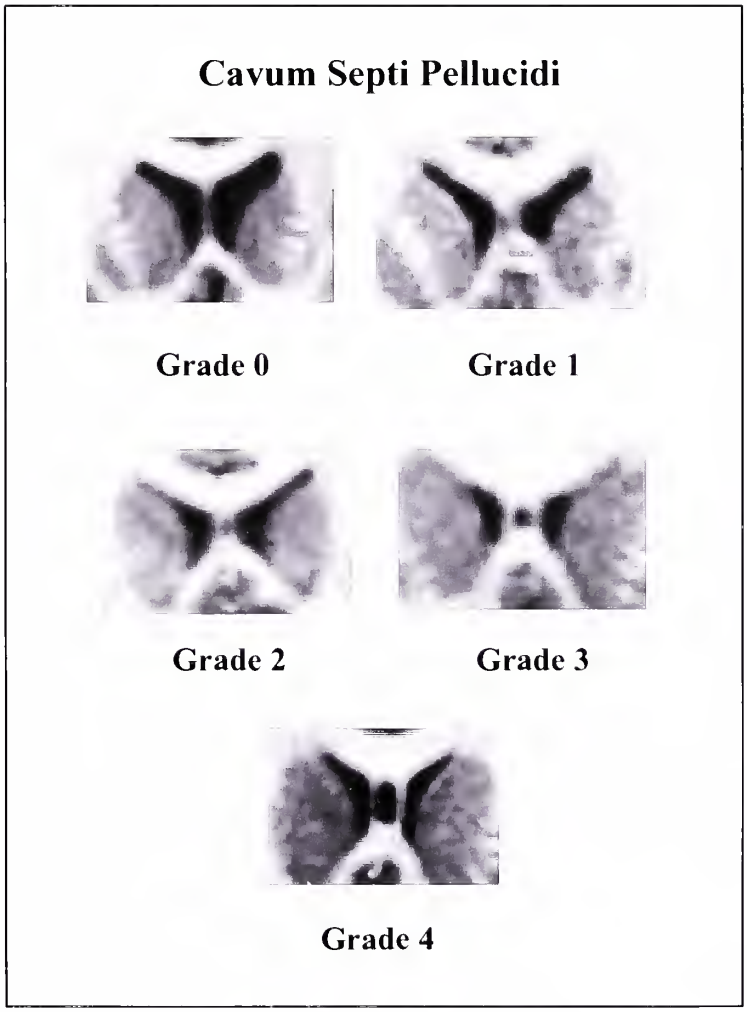
standardized using canthomeatal landmarks. A 3-dimensional-spoiled gradient recall sequence was obtained for analyses of the CSP and CV (repetition time, 24 milliseconds; echo time, 5 milliseconds; flip angle, 45 degrees; frequency encoding superior/inferior; no wrap; 256x192 matrix; field of view, 30 cm; 2 excitations; slice thickness, 1.2mm; and 124 contiguous slices encoded for sagittal slice reconstructions).

CSP Measures

MRI's were analyzed on Sun Ultra 10 workstations using ANALYZE 7.5 software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN; Richard A. Robb, Ph.D., Director). Scans were cropped and magnified 12-fold in each dimension to aid in coding of the CSP. The same observer (K.K.) rated all scans blind to diagnosis and subject characteristics.

Ratings of Coronal Grade. Scans were rated in the coronal view, and the CSP was graded on an ordinal scale of 0 to 4, with descriptive anchors based on the overall size of the visible cavity (0 = absent; 1 = questionable/equivocal; 2 = mild CSP; 3 = moderate CSP; 4 = large CSP). Ratings conformed with previously published methods (36-38) and were performed on the coronal slice that showed the greatest evidence of a cavity. A rating of 0 was assigned if an intact septum pellucidum was clearly visible in all slices (ie. no CSP was present), a rating of 1 was assigned if the septum was unclear (ie. questionable CSP), and ratings from 2 to 4 were assigned based on size of the visible cavity (ie. based on the area, height, and width of the cavity in the coronal view). Reliability of the ratings was aided by comparison with a set of standard CSP images

Figure 1: Images of representative cava septi pellucidi. Each subjects' brain MRI scan was graded on a scale of zero to four based on presence and size of the CSP. A rating of grade 0 was assigned if there was an intact septum pellucidum, grade 1= questionable CSP, grade 2=mild CSP, grade 3= medium CSP, grade 4= large CSP.



from each ordinal grade (see Fig.1). Reliability was quantified using CSP ratings obtained independently from 30 randomly selected scans by two raters familiar with CSP anatomy. Inter-rater reliability was excellent (weighted κ=0.72) (39, 40). The presence of a CV, a potential caudal extension of the CSP (41), was similarly assessed in each scan.

Ratings of CSP Length. The anteroposterior length of the CSP was measured by counting the number of coronal slices containing evidence of the CSP according to previously described methods (42): 0 = absent, 1 = CSP seen in 1 slice only, 2 = CSP seen in 2 slices, etc. The number of coronal slices was multiplied by the width of each image slice to obtain the anteroposterior length of the CSP in millimeters. Reliability between two raters for these length measurements yielded moderate agreement (weighted κ=0.56).

Statistical Analyses

All statistical procedures were performed using SPSS for Windows version 10.0 (Statistical Product and Service Solutions Inc, Chicago, IL). All p-values were of the 2-sided type.

Ratings of CSP size. We tested our primary null hypothesis (that CSP size was not associated with the diagnosis of TS) using ordinal logistic regression with a logit link. Hypothesis testing was performed using the CSP grade primarily, and secondary testing was done with CSP length. Regression analyses were performed first in children (<18 years) and then in an independent sample of adults (18-64 years) in an attempt to replicate findings from the children.

Ordinal ratings of CSP grade were the dependent measure in ordinal regression analyses. The diagnosis of TS was included as the between-subjects factors, and lifetime diagnoses of OCD or ADHD, age, sex, SES at birth, and whole brain volume (WBV) measurements were included as covariates. WBV measurements were included to control for generalized scaling effects within the brain (43). Although handedness and minority status were initially included as possible confounding factors, they were found to have negligible effects on the parameter estimates. Consequently, neither was included in the final models. The same set of regression analyses was then performed entering CSP length as the ordinal dependent measure.

In addition to the above covariates, 2-way and 3-way interactions between diagnosis and covariates were considered for inclusion in the models. Terms that were not significant were eliminated via backward stepwise regression, with the constraint that the model at each step was hierarchically well-formulated (ie. all possible lower order terms must be included in the model regardless of their significance) (44, 45). Two-way interactions between TS and medication use were also entered into the regression model to assess possible medication effects. No interactions were found to be significant, so none were included in the final models.

For each of the continuous covariates (age, SES, WBV), the proportional odds assumption was graphically checked by plotting the cumulative logits of dichotomized ordinal ratings against each covariate (46). Each plot confirmed that the dichotomized responses were linearly related to the covariates, validating use of the ordinal regression modeling for the analyses.

Associations of CSP grade with symptom severity. Symptom severity ratings were available for the majority of TS subjects. Children and adults with TS were combined for these analyses. The associations of CSP grade with the severity of current and worst-ever tic and OCD symptoms, premedicated and current ADHD symptoms, Conners parent and teacher scores, and CBCL scores were explored. Correlations of symptom severity with CSP grade were performed using ordinal regression analysis with CSP grade as the dependent variable, sex as a between-subjects factor, and symptom severity as a continuous covariate. Age and WBV were also entered as covariates.

(*Note:* The recruitment and characterization of the subjects (the structured diagnostic interviews and symptom severity ratings), and the collection of raw MRI scans for this study were performed by other members of the Peterson lab team over the last ten years as part of prior ongoing studies. Review of the existing literature, subsequent development of CSP measures and reliability testing, rating of the 268 MRI scans, CSP data collection and entry, evaluation of medication effects and all statistical analyses were performed exclusively by K. Kim.)

RESULTS

Subjects

High-resolution anatomical brain MRI scans were acquired in 161 children (97 TS subjects and 64 normal controls) and 107 adults (43 TS subjects and 64 normal controls). Amongst the children with TS, 30 (31%) of these subjects also carried lifetime diagnoses of OCD and 29 (30%) had diagnoses of ADHD. In the TS adults, 23 subjects (53%) also had lifetime diagnoses of OCD and 7 (16%) had ADHD.

Amongst the children, the patient group was slightly older than the control group (11.2 ± 2.3 vs. 10.1 ± 2.2 (mean $\pm$ SD), $t_{159} = 2.76$, $p = .06$) and had a higher proportion of males (79.4% vs. 54.7%, $\chi^2 = 11.1$, $p < .001$), but both groups were comparable in terms of SES ($p = .38$). In the adult population, the control group had a higher SES (48.5 ± 9.8 vs. 43.6 ± 11.1, $t_{105} = -2.40$, $p < .02$) than the TS group, but they were similarly aged ($p = .16$) and had similar proportions of males ($p = .96$).

Hypothesis Testing

In analysis of the children only, a diagnosis of TS was a significant predictor of CSP grade in children ($p < .03$, see Table 1a), allowing rejection of our null hypothesis that CSP size was unrelated to diagnosis of TS. The parameter estimate for a diagnosis of TS (PE = -0.77) indicated that these subjects had smaller CSPs than did the control group (see Fig.2a). The covariates of OCD and ADHD were not found to be significant, suggesting that the association of TS with CSP grade was not due to the presence of comorbid OCD or ADHD. WBV was included as a covariate to account for scaling effects, and was associated with CSP grade only at a trend level of significance (PE =

2.71^{E-06}, p = .07). Socioeconomic status, age, and sex were not associated with CSP grade, and did not interact significantly with a diagnosis of TS. Interactions between TS diagnosis and psychotropic medication use, specifically neuroleptic use, were not significant (TS*any medication: PE = .02, p = .98; TS*neuroleptic: PE = .17, p = .73), indicating that medication use did not significantly contribute to our finding of smaller CSPs in the patient group.

Findings were similar when CSP length was entered as the ordinal dependent measure in our regression analyses (see Table 1b). CSP length tended to be shorter in the TS children (PE = -.64, p < .06) compared to healthy subjects. No covariates or interactions were associated significantly with CSP length.

Replication in Adults

In adults, a diagnosis of TS was found to be a significant predictor of CSP grade (p < .05) and CSP length (p < .01) (Table 1a-b). As in the child population, the CSPs in TS adults were smaller and shorter than in control adults (Fig.2b) (CSP grade: PE = -1.05, CSP length: PE = -1.40). Interactions between diagnoses and covariates were not significant and therefore not included in the final model. WBV was the only significant covariate in the CSP grade regression model (PE = 3.68E-6, p < .05), accounting for scaling effects. Age was a significant covariate in the CSP length regression model (PE = .04, p < .04). No significant interactions of TS with neuroleptic or other medication use were detected.

	Children				Adults			
Source	**PE**	**OR**	**SE**	**P-value**	**PE**	**OR**	**SE**	**P-value**
TS	**-.77**	**.17**	**.35**	**<.03**	**-1.05**	**.09**	**.54**	**<.05**
OCD	-.30	.51	.41	.48	.85	7.06	.59	.15
ADHD	-.40	.40	.41	.33	-.76	.18	.81	.35
Age	-.04	.91	.07	.55	.02	1.05	.02	.23
Sex	.68	4.76	.38	.08	.18	1.53	.47	.70
SES	.02	1.05	.01	.11	-.02	.95	.02	.26
WBV	2.71E-6	1.00	<.001	.07	**3.68E-6**	**1.00**	**<.001**	**<.05**

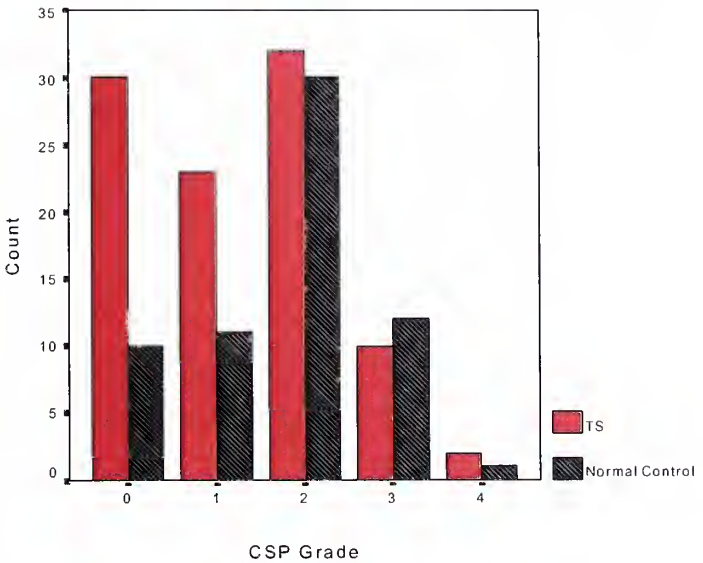
Table 1a: CSP Ordinal Regression Model for CSP Grade. Ordinal logistic regression analysis was used to assess whether diagnosis of TS was a significant predictor of CSP grade in children and adults. Diagnoses of comorbid OCD and ADHD, age, sex and SES were entered as covariates. WBV was also included as a covariate to account for scaling effects. CSP grade was signficantly associated with a diagnosis of TS in both children and adults. Diagnoses of comorbid OCD and ADHD, age, sex and SES were not significantly associated with CSP grade. WBV was significantly associated with CSP grade in the adult model. PE=parameter estimate, OR=odds ratio, TS=Tourette Syndrome, OCD=Obsessive-Compulsive Disorder, ADHD= Attention Deficit Hyperactivity Disorder, SES=socioeconomic status at birth, WBV=whole brain volume.

	Children				Adults			
Source	**PE**	**OR**	**SE**	**P-value**	**PE**	**OR**	**SE**	**P-value**
TS	**-.64**	**.23**	**.34**	**<.06**	**-1.40**	**.04**	**.54**	**<.01**
OCD	-.03	.92	.40	.93	.84	6.91	.59	.15
ADHD	-.15	.71	.39	.71	-.78	.17	.81	.34
Age	-.04	.92	.06	.55	**.04**	**1.08**	**.02**	**<.04**
Sex	.58	3.81	.37	.11	.53	3.40	.47	.25
SES	.02	1.04	.01	.23	-.03	.94	.02	.19
WBV	2.62E-6	1.00	<.001	.07	2.45E-6	1.00	<.001	.18

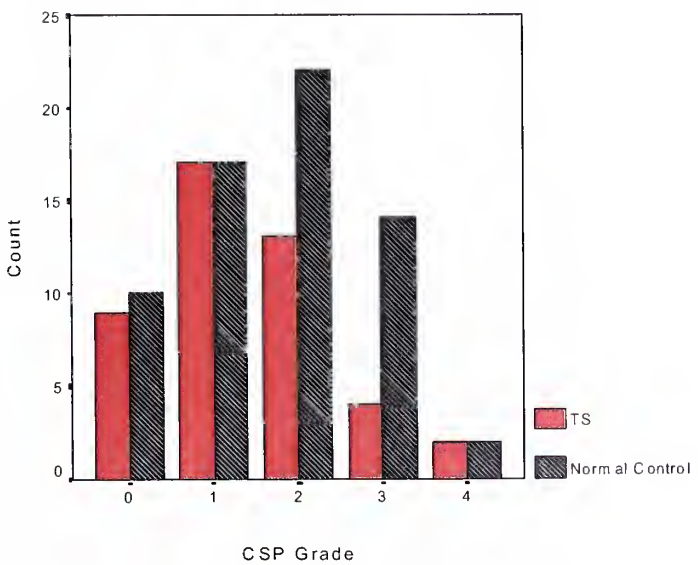
Table 1b: CSP Ordinal Regression Model for CSP Length. Estimated CSP length was associated with a diagnosis of TS in both children and adults. Diagnosis of comorbid OCD and ADHD, sex, SES and WBV were not significantly associated with CSP length. Age was significantly associated with CSP length in the adult model only. Abbreviations are as in Table 1a.

Figure 2: Frequency Distributions of CSP Grade in patients and normal controls. These plots display the number of TS patients versus control subjects rated in each ordinal category of CSP grade. The control subjects are distributed approximately normally between grades 0 and 4, while the patients' grades are shifted to the left. TS = Tourette Syndrome.

2a. Children



2b. Adults



Associations with Symptom Severity

In TS children and adults, CSP grade was significantly associated with the pre-medicated severity scores for ADHD inattention and combined-type symptoms (inattention: PE = -.12, $p < .002$, N = 64; combined-type: PE = -.06 , $p < .003$, N = 64). For subjects with TS, including those with comorbid OCD or ADHD, having a smaller CSP was associated with more severe premedicated ADHD symptoms. CSP grade was not significantly associated with the severities of current ADHD symptoms, nor with tic or OCD symptoms.

Additional Characterization of the CSP and CV

In the children, 30 patients (31%) and 10 normal controls (16%) had no CSP (ie. Grade 0), while 44 patients (51%) and 43 normal controls (67%) had mild, moderate, or large CSPs (ie. grades 2-4). One child with TS and ADHD had a CSP of grade 4 with a CV. In the adult population, 9 TS (21%) and 10 normal controls (16%) had no CSP, while 16 TS subjects (37%) and 38 normal controls (59%) had CSPs of grade 2-4. Two of the adult normal controls and one TS subject with OCD had a CSP of grade 4 with a CV. The presence of a CV was not significantly associated with a diagnosis of TS (Fisher's p = 1.0 for children and adults).

DISCUSSION

The aims of this study were to characterize the CSP in TS subjects and to assess whether symptom severity was related to CSP size. We found that the CSP in TS children was smaller than in normal control children, using both CSP grade and estimated CSP length as indicators of CSP size. We then replicated these findings in an independent sample of TS and normal adult subjects. CSP grade and length were not significantly associated with a lifetime diagnosis of comorbid OCD or ADHD, sex, or socioeconomic status. Age was only significantly associated with CSP length in the adult group. Neuroleptic or other psychotropic medication use did not seem to contribute to the finding of smaller CSPs in TS subjects.

CSP grade was also significantly related to the severity of ADHD inattention and combined-type symptoms in TS subjects prior to beginning medications. CSP grade was not associated, however, with the severity of current ADHD symptoms, tic, or OCD symptoms.

In addition to the findings in TS subjects, this study provides normative data on CSP size in a large, community-based sample of healthy children and adults. Previous prevalence estimates in normal adults has ranged widely from 2% to 85% (8, 36, 41, 47, 48). This variability in previous prevalence estimates has several likely sources. First, most prior studies regarded the CSP dichotomously as either "enlarged" (and pathological) or "within normal limits," and the criteria for this rating varied considerably across studies. Second, most prior studies have been either postmortem investigations, in which fixation procedures can alter CSP morphology, or lower resolution imaging studies that could underestimate the prevalence of small CSPs. Third, prior studies have drawn

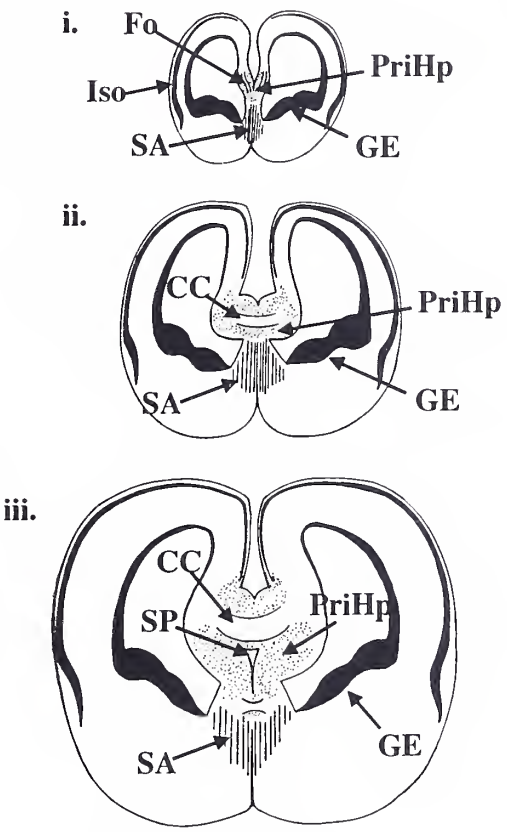
subjects from heterogeneous clinical populations, where CSPs tend to be larger and more variable (49). In contrast, the present study employed measures from high-resolution scans obtained in a large community sample of healthy subjects. These methodological advantages are probably why the data from this sample were able to reveal that CSP size in the general population is likely to be continuous and normally distributed (Fig.2). The underlying normal distribution of CSP size is presumably a direct consequence of normal variability in CSP closure during early development. In addition, our results suggest that the distribution of CSP sizes is similar in children and adults (50, 51), consistent with the determination of CSP size early in development.

Embryology of the Septal Region

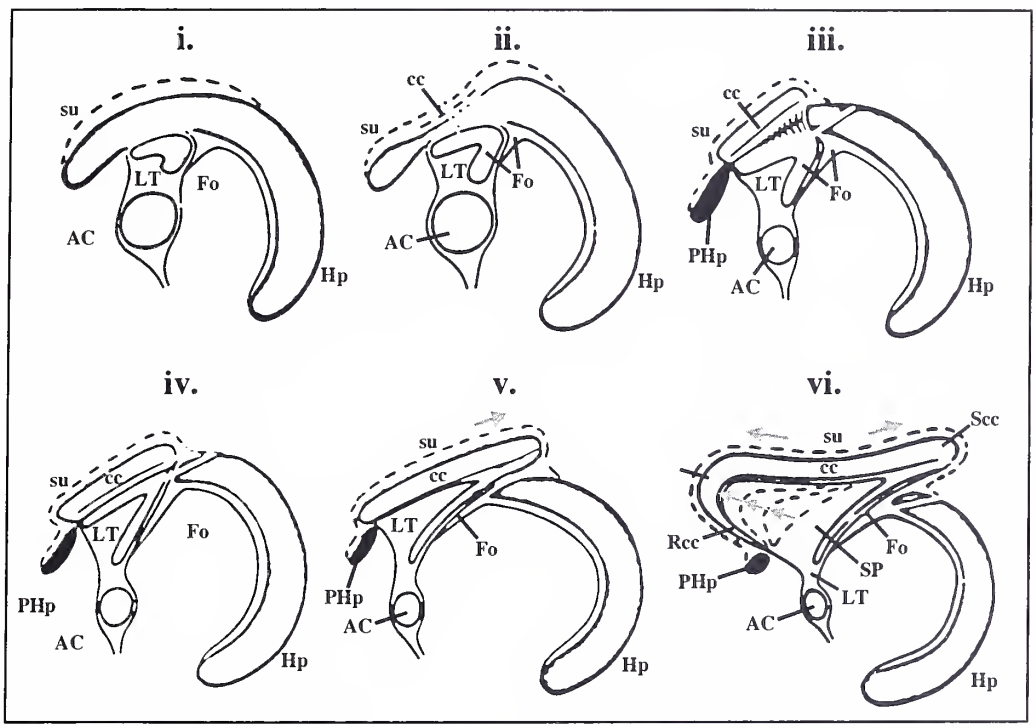
The embryology of the CSP and the associated septal region is relevant to understanding the significance of these findings for the pathophysiology of TS. The CSP first appears in week 12 of gestation. It begins as a hollowing of the solid lamina terminalis beneath the primordial hippocampal tissue. Initially, differential growth of the neighboring corpus callosum is thought to stretch and progressively thin the lamina terminalis to form a clear membrane, the septum pellucidum. Continued growth of the corpus callosum further stretches the septum pellucidum to produce a midline cleavage (47, 49, 52, 53) (see Fig.3a-b). Invasion of circulating phagocytic monocytes may help to cavitate the septum to create the CSP (54, 55). The leaves of the septum pellucidum now laterally bound the CSP on each side.

Figure 3: CSP embryology and development.

3a. Development of the corpus callosum and cavum septi pellucidi (coronal view). i) Juxtaposition of the banks of the median sulcus, and formation of the massa commissuralis in the region of the primordial hippocampus (PriHp) in the floor of the interhemispheric fissure. ii) The commissuration of the hemispheres by fibers of the corpus callosum (CC) and rostral extension of the massa commissuralis over the median sulcus. iii) Separation of the banks of the median sulcus forming the leaves of the septum pellucidum (SP). The CSP is sealed inferiorly by the rostrum of the corpus callosum. Fo=fornix, Iso=isocortex, SA=septal area, GE=ganglionic eminence. (53)



3**b. Phylogenetic development of the septal region (sagittal view).** Development of the CSP in humans roughly recapitulates phylogenetic development. i) Marsupials: The hippocampus (Hp) and subiculum (su) are dorsal to the lamina terminalis (LT). ii) Intermediate stage: The hippocampus begins to infold. iii) Hedgehog and bat: The corpus callosum (cc) and fornix (Fo) have broken through the subiculum. iv and v) Rat: The intercommissural hippocampus has been obliterated, leaving only the pre- and post-commissural parts. vi) Humans: The corpus callosum grows lengthwise in the direction of the arrows, and the septum pellucidum (SP) stretches anteriorly. PHp=precommissural hippocampus, AC=anterior commissure, Rcc=rostrum of CC, Scc=splenium of CC, Gcc=genu of CC. (49)



At approximately the 20th week of gestation, the leaves of the septum pellucidum fuse in the posterior to anterior direction, probably as a consequence of continued growth of the anterior portion of the corpus callosum and hippocampal alvei (3, 41). Growth of the rostrum of the corpus callosum apposes the inferior aspect of the two leaves of the septum pellucidum and subsequently seals the CSP inferiorly. Cells migrating inward from the lateral septal nuclei then populate the CSP (54, 55). CSP closure reaches its

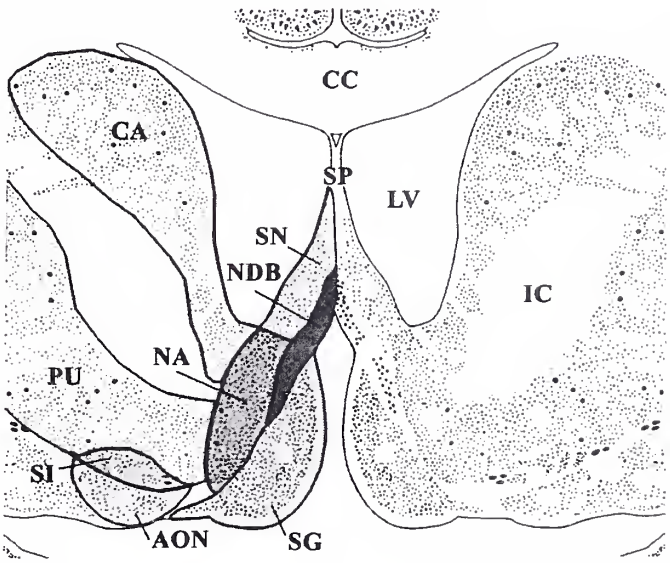
adult state in the majority of children by 6 months of age (1). Whether structural plasticity in the surrounding septal tissue can alter CSP morphology subsequently in development is unknown.

The formation and resolution of the CSP is therefore intimately linked with concurrent development of the corpus callosum, hippocampus, amygdala, and septal nuclei. Disturbances of CSP anatomy in children and adults could thereby reflect embryological abnormalities in the development of these neighboring structures. Given the possible relevance of these multiple neighboring regions in determining CSP morphology, focusing solely on either the CSP in the coronal view or on its anteroposterior length (as many previous studies have done) may offer an incomplete view of CSP pathology. The degree of non-closure of the CSP in the lateral and superior-inferior dimensions (ie. the width or height of the cavity) along with its anteroposterior length may jointly provide important clues to altered CNS development.

Septal Anatomy and Function

The septal region is an important component of the limbic system that has widespread connections to other regulatory centers in the brain (see Fig.4). It serves as a key relay station between the hypothalamus, hippocampus, amygdala, and brainstem (56). These septal circuits are thought to play an important role in numerous biological and behavioral systems, including self-maintenance, sensory processing, attention and activity, memory and learning, sexuality, aggression, homeostasis, emotionality, and maternal behavior (3, 57-59). Abnormal development of the septal region therefore may disrupt one or more of these functions.

Figure 4: Anatomy of the septal region. The septal nuclei are located inferolateral to the septum pellucidum. These nuclei, part of the limbic system, relay fibers between the brain stem, hippocampus, amygdala, habenula, hypothalamus, mamillary bodies, substantia nigra, cingulate gyrus, forebrain, and cortex. The medial septal nuclei are primarily output nuclei and include the nucleus of the diagonal band of Broca, the bed nucleus of the stria terminalis, the bed nucleus of the anterior commissure, and the septofimbrial nucleus. The lateral septal nuclei are primarily input nuclei and include the nucleus basalis of Meynert and the nucleus accumbens (56). The brain is represented here in a coronal view. CA=caudate nucleus, PU=putamen, SP=septum pellucidum, SN=septal nuclei, NDB=nucleus of the diagonal band of Broca, CC=body of the corpus callosum, NA=nucleus accumbens, SI=substantia innominata, AON=anterior olfactory nucleus, SG=subcallosal gyrus, IC=internal capsule, LV=lateral ventricle, frontal horn. (60)



The septal nuclei and related limbic system circuits are interconnected with many of the brain regions implicated in the pathophysiology of TS-related disorders (15). The sexual and aggressive content of many tics, obsessions, and compulsions, for example, suggests involvement of these systems in TS and OCD. The septal nuclei are thought to help filter sensory input, and lesions in this region have resulted in increased motoric activity and hyperreactivity to stimuli (59, 61, 62). Related limbic circuits could thereby contribute to the attentional and motor abnormalities in TS and ADHD. The regions with

the strongest anatomical connections to the septal nuclei, such as the cingulate cortex, temporal lobe, hypothalamus, and periaqueductal gray, are limbic system components that have previously been hypothesized to contribute to the appearance and modulation of TS-related symptoms (63-67).

Pathophysiology

The finding of smaller CSPs in a patient population has not been reported previously. It highlights the importance of considering the role of the developing CSP and associated septal nuclei in the pathogenesis of TS. A smaller CSP in TS patients could arise from disturbances in the formation of the CSP, from excessive or premature closure of the CSP, or as a consequence of potential postnatal plastic changes in septal tissue surrounding the CSP. The timing of these developmental abnormalities, whether early or late in life, are key to determining what role the altered CSP morphology might play in the pathophysiology of TS.

The embryological origins of the CSP suggest that smaller CSPs could be a consequence of an initial failure of the corpus callosum to develop properly during gestation. It may therefore be relevant that abnormalities in corpus callosum morphology have been reported in both TS children and adults (68, 69). Alternatively, smaller CSPs could arise secondary to a genetic or environmental event during the pre- or perinatal period that exaggerates CSP closure. Peri- or postnatal plastic changes in the septal area that preferentially affect TS subjects could also produce localized septal hypertrophy and therefore smaller CSPs (43). Similarly, hypertrophy of neighboring structures potentially involved in TS pathophysiology (such as the thalamus or hypothalamus) could contribute

to increased closure rates for the CSP. Finally, postnatal fibrosis and gliosis in the septal region, perhaps a consequence of autoimmune processes that have been suspected in some cases of TS (70, 71), could produce CSP narrowing.

The pathophysiological relevance of the association of CSP grade with the severity of premedicated ADHD symptoms in TS subjects is unclear. CSP size may reflect alterations in septal tissue or related brain regions that help modulate the severity of ADHD symptoms. The association therefore suggests that early developmental events may contribute to ADHD comorbidity in TS subjects. Because ADHD (unlike OCD) is unlikely to be a variant expression of an underlying TS genetic diathesis (14, 72), these early developmental events that influence ADHD comorbidity in TS seem likely to be of a nongenetic origin. CSP size may also be associated nonspecifically with ADHD symptom severity (ie. regardless of the presence of tics). The group specificity of these associations therefore requires further study in larger samples of OCD and ADHD subjects.

Limitations and Future Directions

This study points to the likely importance of early developmental events in the pathophysiology of TS. Future studies will need to focus on these early events to determine which pre- and peri-natal complications might affect both the size of the CSP and the course of illness. Our findings suggest that the limbic system may be an increasingly important, though heretofore relatively neglected, area of TS research. The CSP, however, offers only an indirect assessment of the development of the septal region and its associated limbic structures. More detailed morphometric and functional imaging

studies as well as postmortem examinations are needed to define better the sequelae of disturbances in septal and limbic system development in TS. Studies of the nucleus accumbens, hippocampus, amygdala, cingulate, hypothalamus, and brain stem nuclei may therefore be informative in TS research, as they all have strong connections to the septal nuclei. They would complement the current findings and further elucidate the role of the limbic system in the pathophysiology of TS.

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